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(54) Title: HORMONE REPLACEMENT THERAPY DRUG FORMULATIONS FOR TOPICAL APPLICATION TO THE SKIN

(57) Abstract

Topical alcoholic or aqueous alcoholic gels containing testosterone, progesterone, estradiol or other hormones have enhanced penetration through skin by including in the formulation 2–n–nonyl–1,3–dioxolane or other hydrocarbyl derivative of 1,3–dioxolane or 1,3–dioxane or acetal, as skin penetration enhancing compound.

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HORMONE REPLACEMENT THERAPY DRUG FORMULATIONS FOR TOPICAL APPLICATION TO THE SKIN

FIELD OF INVENTION

This invention relates to topical compositions for transdermal administration of a hormone through the skin of a patient and to the method for transdermally administering the hormone using the topical composition.

DISCUSSION OF THE PRIOR ART

All drugs must be administered in such a manner that they reach the intended site in the body in an optimal concentration (e.g., amount of drug per unit volume of blood) to achieve the desired effect at the proper time, and for an appropriate length of time. Customarily, drugs are taken orally, injected, inhaled, or applied topically. These conventional routes of administration often fail to meet the stated objectives, however. For example, when drugs are absorbed into the blood stream by whatever route, peaks and valleys in the blood concentration of the drug occur and may cause undesirable effects (e.g., peak levels), or loss of activities (e.g., valleys). To meet these problems, a variety of approaches have been investigated. These include, for example, special drug coatings, combining the drug with other materials, suspensions or emulsions, and compressed tablets. Although these formulations attempt to control the release of drugs from their carriers, the desired effects are often not reproducible, may be subject to patient-to-patient variations, and may not be suitable for prolonged periods of delivery, such as days or even months.

Recent research has produced systems in which a drug is implanted in the body, released from skin sites, introduced in to the body by minipumps, and/or released in minute quantities through the skin. These innovative drug-delivery systems are improving drug effectiveness and also are opening opportunities for new pharmaceuticals.

The administration of drugs and other biological materials to the bloodstream via a transdermal route of administration has received much attention in recent years. The skin of an average adult covers more than two square meters of surface area and receives about one-third of all blood circulating through the body. It is elastic, rugged, and generally self-generating. The skin consists of three layers: the stratum corneum (S.C.), the epidermis, and the dermis. The stratum corneum represents the rate-limiting step in diffusion of chemical through the skin. The S.C. is composed of dead, keratinized, metabolically inactive cells which are closely packed together, and consists of an amorphous matrix of mainly lipoid and nonfibrous protein within which keratin filaments are distributed. The cells of the S.C. generally contain 20% water, while the cells below, in the stratum germinativum, contain 70% water. The S.C. does not become hydrated readily. Thus, transdermal permeation is primarily controlled by diffusion through the S.C.

There are several major reasons for the interest in transdermal delivery of drugs:

- elimination of uncertainties of absorption from, and irritation to, the gastrointestinal tract which arise when drugs are administered orally.
- bypassing the portal circulation, thereby eliminating first-pass metabolism in the liver; this is extremely important for drugs with short half-lives, or with potential unwanted actions on the liver.
- delivery of medication directly into the systemic circulation at a constant rate (similar to intravenous infusion).
- infrequent dosing (daily, weekly or longer) for certain drugs.
- ease of use; foster patient compliance.

However, present transdermal delivery systems often have major drawbacks. For example, they are restricted to low-molecular weight drugs and those with structures having the proper lipophilic/hydrophilic balance. High molecular weight drugs or drugs with too high or low hydrophilic balance often cannot be incorporated into current transdermal systems in concentrations high enough to overcome their impermeability through the stratum corneum.

Transdermal delivery is generally restricted to those medications requiring delivery rates less than 10 mg/day. In order to obtain higher blood levels, the rate of drug delivery must be increased. There have been many proposals to accomplish the higher rate of drug delivery via the use of absorption promoters and by the development of prodrugs that can be more readily absorbed. Examples of existing absorption enhancers include dimethyl sulfoxide (DMSO), ethylene glycol, hexanol, fatty acid and esters, and pyrrolidone derivatives, among others. One such enhancer compound which has received much attention is Azone (N-dodecyl azacycloheptan-2-one).

One of the present applicants has previously developed a new class of compounds which are derivatives of 1,3-dioxanes and 1,3-dioxolanes for use as skin penetration enhancing compounds. These compounds, which have been made commercially available under the trademark SEPA®, are described in detail in U.S. Patent No. 4,861,764. Work with the dioxolane enhancers has been described in several literature and patent publications. For example, Samour, et al., *Proc. Int. Symp. Control. Rel. Bioact. Mater.* 16: 183-184 (1989); Marty, et al., *Proc. Int. Symp. Control. Rel. Bioact. Mater.* 16:179-180 (1989); Marty, et al., *Proc. Int. Symp. Control. Rel. Bioact. Mater.* 17:415-416 (1990); Michniak, et al., *Drug Delivery* 2:117-122 (1995); Marty, et al., Abstract of Paper Presented at American Association of Pharmaceutical Scientists, Washington, D.C., March 26-28, 1990.

While there are many prior art patent and literature disclosures of topical hormone delivery systems, including, for examples, formulations for topically delivering testosterone, there has not, to date, been any commercially available non-patch topical testosterone or other hormone products. Other topical hormone products are still not sufficient. There are however, a few commercially available transdermal hormone delivery patch products which are commercially available, for example, Androderm®, from Theratech and Testoderm®, from ALZA Corp, for testosterone; Estraderm®, from Ciba Pharmaceutical, for estradiol. All of these products which are currently available in the United States are of the infinite dose type in contrast to the European Oestrogel® which is of the finite dose type.

The reasons that commercial topical (e.g., gel, cream, ointment) products have not become readily available or are not entirely satisfactory, are not always known. Undoubtedly, it is the result of several factors. For example, it is believed, in general, that the prior disclosures and attempts to produce topical hormone replacement therapies have not been successful due to the inability to adequately and stably target the intended site with therapeutically effective dosages in a reasonable period of time. In addition, effective carrier systems, including, for example, solvents for the hormonal drug of interest and suitable percutaneous penetration enhancers, having the requisite product stability and drug delivery profiles, generally cannot be developed based simply on the knowledge of carrier systems in topical formulations for other specific drugs or even from the carriers for patch systems from the same drug.

While transdermal patch delivery systems often provide some advantages, they all rely on particular adhesive layers for adhering the patch to the target site and, therefore, for at least some patients, can result in irritation, while for other candidate patients with, for example, excessively oily or tender skin, or for hairy skins, patches may not be

applicable. Patch delivery systems differ from topical formulations in that drug delivery with the former is membrane diffusion controlled whereas drug delivery with the latter is thermodynamically controlled. Therefore, a topical formulation to be applied directly to the skin, in the form of, for example, gel, ointment, or cream, would be highly advantageous. However, to be feasible, such topical formulation should be easy to apply without being too runny, greasy, or otherwise messy to use by the patient. Furthermore, since topical gel formulations, as contemplated herein, provide a finite dose of the medicament, it is necessary to maintain a relatively uniform (e.g., high) flux of the medicament over time even as the concentration of the medicament in the gel decreases over time.

The present invention provides a solution to the above problems using the hydrocarbyl-group substituted 1,3-dioxolanes, 1,3-dioxanes and acetals as skin penetration enhancers (SPE), which have been formulated with carrier systems designed to effectively solubilize both the hormonal drug and the skin penetration enhancer; provide long shelf-life and stability; remain on the skin for extended periods of time; and effectively and consistently provide the desired drug delivery profile for a particular drug and particular patient (e.g., skin type; dosage requirement, etc.); and further, without requiring any particular device or patch or other adhesive based system.

In particular, the present inventors have continued to study the effect of the 1,3-dioxane and 1,3-dioxolane derivatives and related acetals as skin penetration enhancer (SPE) compounds for various hormonal compounds. Surprisingly, it has been found that this class of SPE compounds provides better drug delivery profiles than the commercially available patch systems for hormone replacement therapies. For example, as will be shown in the examples to follow, if the gel from a commercially available patch reservoir system is removed and applied as a finite film on the skin in the same manner as for the topical gels of this

invention, the flux of the former is greatly reduced as compared to that of the latter. Accordingly, the gel from the reservoir system would not be effective as a topical product and must be presented as a reservoir system in order to overcome this fundamental drug delivery problem. This then necessitates the application of a patch which must remain in place for prolonged periods, in turn exacerbating such problems as irritation, user non-compliance, and the like. Moreover, delivery may still be less than is attainable by the present gels.

SUMMARY OF INVENTION

The present invention has as a principal object to provide stable topical compositions effective for the transdermal application of hormone compounds by the application of the composition to the skin.

The composition of this invention is a hormonal drug containing alcoholic or aqueous alcoholic composition which comprises, on a weight basis, of the total composition:

a therapeutically effective amount of from about 0.1 to about 10% of hormonally active drug;

a skin penetration enhancing effective amount, in the range of from about 2 to 20%, of a C_7 to C_{14}-hydrocarbyl substituted 1,3-dioxolane, 1,3-dioxane or acetal (which may hereinafter be collectively referred to as SPE);

0 to about 25% of 1,2-propylene glycol;

from about 35% to 75% of volatile alcohol selected from ethanol, isopropanol and mixture thereof;

0 to about 35% water; and,

optionally, a gelling agent effective to thicken the composition to avoid or minimize run-off when applied to the skin.

Furthermore, the formulations according to the invention are preferably further characterized by an average *in vitro* flux greater than about 5 $\mu g/cm^2/day$, preferably greater than about 10 $\mu g/cm^2/day$ and especially preferably, greater than about 20 $\mu g/cm^2/day$, and usually up to as high as about 40 $\mu g/cm^2/day$.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a ternary phase diagram showing the miscibility of 2-n-nonyl-1,3-dioxolane skin penetration enhancer in an ethanol-propylene glycol-water vehicle;

Fig. 2 is a ternary phase diagram showing the miscibility of the 1,3-dioxolane skin penetration enhancer in an isopropanol-propylene glycol-water vehicle;

Fig. 3 is a graph plotting the cumulative absorption of estradiol, as percent of dose versus time, from a gel according to the invention (▲), a similar gel but without the skin penetration enhancer (•); or from a commercial product (▪);

Fig. 4-A is a graph plotting flux of estradiol versus time in an *in vitro* study for an aqueous alcoholic gel according to the invention containing 2 wt.% estradiol, and 10 wt.% of 2-n-nonyl-1,3-dioxolane (2-NND) skin penetration enhancer (○), or a similar control gel containing 2 wt.% estradiol but without skin penetration enhancer (□), or a similar gel containing 2 wt.% estradiol and 10 wt.% of a different skin penetration enhancer, laurocapram (Azone®) (▲).

Fig. 4-B is a graph plotting Payload (cumulative diffusion) as percent of dose of estradiol versus time for the same samples used in the study of Fig. 4-A; and

Fig. 5 is a graph plotting the cumulative delivery of testosterone through human skin versus time *in vitro* for two gel formulations; one according to the invention, non-occluded, containing 10 wt.% 2-NND (▪) and the other being the gel contained within the commercially available Androderm® patch, placed under occlusion (▲) or without occlusion (•).

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

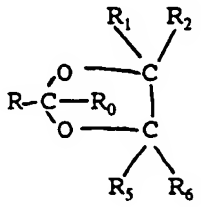
The compositions of the invention are intended for topical, non-invasive, application to the skin, particularly to those regions of the skin, e.g., inside arm, back, etc., providing maximal systemic absorption of the hormonal active ingredient.

Examples of the hormonal drug (hormone) which is advantageously administered by the topical formulations of this invention include, for example (with typical indications shown in parentheses) Androgens, such as, for example, androstenediol and androisoxazole (for anabolic disorders), testosterone (hypogonadism, muscle wasting, male impotence, postmenopausal symptoms in women), dihydrotestosterone (hypogonadism, muscle wasting), dehydroepiandrostenone (muscle wasting, fat reduction, fitness); estrogens (postmenopausal symptoms, birth control), such as, for example, 17 beta-estradiol, estradiol-3,17-diacetate, estradiol-3-acetate, estradiol-17-acetate, estradiol-3,17-valerate, estradiol-3-valerate, estradiol-17-valerate, ethinyl estradiol, estrone; progesterones (prevent endometriosis, prevent endometrial cancer, control habitual abortion, suppress or synchronize estrus, promote hair growth), such as, for example, progesterone (preg-4-ene-3,20-dione), norethindrone, norgestrieone, norgestadienone, norgestrel, norgestimate, progestogenic acid, dihydroprogesterol, nomagesterol. Furthermore, in the above listed exemplary hormones, the testosterone hormone may be used in any of its usual forms, such as, for example, acetate, propionate, 17-beta-cyclopentane-propionate, enanthanate, isobutyrate, undeconate, and the like. Similarly, the estradiols may additionally be used in any of the known or newly developed forms, such as, for example, pivalate, propionate, cypionate, benzoate and other esters. Among these, especially preferred, based on the current level of knowledge in the pharmacological arts, are testosterone, progesterone and estradiol, in any of the salt or ester forms.

More generally, however, any of the government approved hormones, such as listed in, for example, the most current edition of The Merck Index, may be advantageously used.

The penetration of the active ingredient through the skin is enhanced to an acceptable level by including in the composition a skin penetration enhancing effective amount of an SPE of the substituted 1,3-dioxacyclopentane and substituted 1,3-dioxacyclohexane types disclosed in U.S. 4,861,764, the disclosure of which is incorporated herein in its entirety by reference thereto, or the corresponding substituted acetal compound. Representative examples of the skin penetration enhancing compounds include:

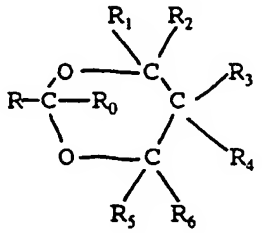
2-substituted 1,3-dioxolanes of the formula (I):



(I)

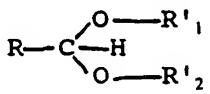
,

2-substituted 1,3-dioxanes of the formula (II):



(II)

substituted-acetals of the formula (III):



(III)

In the above formulas (I), (II) and (III) R preferably represents a C_7 to C_{14} hydrocarbyl group,

R_0, R_1, R_2, R_3, R_4, R_5, and R_6, each, independently, represent hydrogen or a C_1 to C_4 alkyl group.

R'_1 and R'_2, each, independently, represent C_1 to C_4 alkyl group.

The hydrocarbyl group for R may be a straight or branched chain alkyl, alkenyl or alkynyl group, especially alkyl or alkenyl. Preferably, R represents a C_7 to C_{12} aliphatic group; especially C_7 to C_{10} aliphatic group. Examples of suitable alkyl groups include, for example, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, 2-methyl-octyl, 4-ethyl-decyl, 8-methyl-decyl, and the like. The straight chain alkyl groups, such as n-heptyl, n-octyl, n-nonyl and n-decyl, are especially preferred. Examples of alkenyl groups include, for example, 2-hexenyl, 2-heptenyl, 2-octenyl, 2-nonenyl, 2',6'-dimethyl-2',6'-heptadienyl, 2'6'-dimethyl-2'heptaenyl, and the like. The R group may also be substituted by, for example, halo, hydroxy, carboxy, carboxamide and carboalkoxy.

The C_1 to C_4 alkyl group may be, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and the like. The preferred alkyl groups for R_0, and for R_1 to R_6 and for R'_1 and R'_2 are alkyl having 1 or 2 carbon atoms, most especially ethyl. R_0, and R_1 to R_6 may also, preferably, all be hydrogen.

Specific enhancer compounds include, for example, 2-n-heptyl-1,3-dioxolane, 2-n-nonyl-1,3-dioxolane, 2-n-undecyl-1,3-dioxolane, 2-n-nonyl-1,3-dioxane, 2-n-undecyl-1,3-dioxane, 2-n-heptylaldehyde-acetal, 2-n-octyl-aldehyde-acetal, 2-n-nonylaldehyde-acetal, 2-n-decylaldehyde-acetal, 3,7-dimethyl-2,6-octadienal (citral), citronal and the like. 2-n-nonyl-1,3-dioxolane (2-NND) is especially preferred.

The amount of the enhancer compound is selected to provide the desired delivery rate for the active compound but, taking into consideration such additional factors as, product stability, side effects, carrier system and the like. Generally, depending on the particular hormone and other vehicles, amounts in the range of from 2 to 20%, preferably from about 2 or 3 to 12 or 15 percent, especially from about 5 to 10 percent, of the composition, will provide optimal flux rate and 24 hour payload of the active ingredient.

For any particular formulation the hormone and other ingredients may be selected to achieve the desired drug delivery profile and the amount of penetration desired. The optimum pH may then be determined and will depend on, for example, the nature of the hormone, the base, and degree of flux required. Generally, neutral to slightly basic pH's are preferred, in view of the stability of the dioxolane, dioxane and acetal compounds at these pH's.

The compositions are generally formulated as gels, especially aqueous-alcoholic gels. However, other forms, such as, for example, lotions, creams, mousses, aerosols, ointments, etc., may be used so long as when applied to the affected or desired area of the skin the formulation will stay in place, i.e., without run-off, for sufficient time, to permit an individual to spread and retain the composition over and on the skin.

The vehicle for any of the forms of the compositions of the invention will usually include a diol, particularly, 1,2-propylene glycol, other 1,2-diols, such as, for example, 1,2-butylene glycol, 1,2-hexylene glycol, etc., may also be used. The vehicle also includes lower alcohol, e.g., ethanol, and/or isopropanol, and, usually, water. A thickening or gelling agent is also usually and preferably included to facilitate application of the formulation to the skin. In addition, of course, the skin penetration enhancing dioxolane, dioxane or acetal is included in the formulations in an amount effective to enhance the penetration of the active hormone ingredient through the skin, including the stratum corneum.

Accordingly, the vehicle or carrier system for the hormone and enhancer components is preferably an aqueous or non-aqueous alcoholic carrier containing sufficient alcohol, especially ethanol and/or isopropanol and, usually, 1,2-propylene glycol, to solubilize the hormone and be miscible with the SPE. Generally, however, depending on the amounts of SPE and hormone in the formulations the aqueous alcoholic carrier can contain from about 35% to about 70% of ethyl

alcohol and/or isopropyl alcohol, preferably, from about 50 to about 70 percent of ethanol or from about 45 to 55 percent of isopropanol. Mixtures of ethanol and isopropanol in proportions providing the desired solubility of hormone and compatibility with the SPE can also be used. More generally, however, the present inventors have developed miscibility data for combinations of alcohol (ethanol or isopropanol), 1,2-propylene glycol and water for one specific SPE, namely, 2-n-nonyl 1,3-dioxolane (2-NND). This data is graphically represented by the ternary phase diagrams provided as Figure 1 (for ethanol) at 2 wt.% (•) and 10 wt.% (▪) of 2-NND and Figure 2 (for isopropanol) at 2 wt.% (O) and 10 wt.% (•) of NND. In each of these phase diagrams, the upper portions (above the lines connecting the data points) represent the proportions at which the vehicle components are miscible with each other and with the SPE; conversely, the region below the lines connecting the data points represent the proportions where the vehicle components are immiscible.

Again, the total amount of the aqueous or non-aqueous, alcoholic carrier will depend on the amount of hormone, amount and type of SPE, and the form of the composition, e.g., gel, cream, ointment, etc. Usually amounts of the aqueous or non-aqueous alcoholic carrier within the range of from about 70% to about 95% may be used.

In the preferred compositions which are in the form of a gel, a thickening agent, such as hydroxypropyl cellulose, will be included as a gelling agent. However, any other pharmaceutically acceptable thickening/gelling agent may be used. For example, mention may be made of other cellulosic ethers, polymeric thickening agents, e.g., acrylic acid polymers, Carbopol® thickeners, etc., xanthan gum, guar gum, and the like, as well as inorganic thickeners/gelling agents. The amount of the thickening agent is not particularly critical and can be selected to provide the desired product consistency or viscosity to allow for easy application to the skin but which will not be too watery or

loose so that it will stay where applied. Generally, depending on its molecular weight, amounts of thickening agent up to about 5%, preferably, up to about 4%, such as, for example, from 0.1 to about 2% or 3%, of the composition will provide the desired effect.

As is also well known in this art, it is possible to include other ingredients in the formulations for particular aesthetic and/or functional effects. For example, the formulations may, optionally, include one or more moisturizers for hydrating the skin and emollients for softening and smoothing the skin. Glycerin is an example of such a suitable moisturizing additive. When present the additive will usually be incorporated in an amount of up to about 5 percent by weight of the composition, for example, from about 0.1 to 5%.

The effects of the topical compositions according to the invention are further illustrated by way of the following representative examples which in no way are intended to limit the scope of the invention.

Example 1

This example compares the percutaneous absorption through human skin of progesterone (preg-4-ene-3,20-dione) from aqueous alcoholic gels or solutions containing from 1 to 6 wt.% progesterone and 0 or 5%, 10% or 15% of 2-n-nonyl-1,3-dioxolane (2-NND), using an ethanol/propylene glycol/water carrier at a 70:20:10 mixing ratio (except as noted). Hydroxypropyl cellulose (2 wt.%) is used as the gelling agent in the gel formulations. The test compositions are applied to provide about 30 milligrams (mg) of the composition per square centimeter (cm^2) of human skin.

The tests are run in standard static cells with phosphate buffered saline (PBS) and ethanol mixture (80:20) as the receptor fluid (surface area 0.635 cm^2, temperature 32°C). The following Table 1 shows the total amount of progesterone, enhancer (2-NND), ethanol (E), 1,2-propylene glycol (PG) and water for each formulation.

Each test was run for 24 hours under non-occluded conditions with the finite dose of the test formulation.

Table 1

Run No.	Type	Progesterone wt. %	2-NND wt.%	Peak Flux $\mu g/cm^2/hr$	24 hour %-dose
1	gel	2	0	1.9	10
2	gel	2	0	6	6
3	solution	6	0	8	8
4	gel	2	5	4	7.5
5	gel	1	5	3.6	9
6	gel	2	5	3.2	8.8
7	solution	2	5	2.3	8
8	solution*	2	10	4	13
9	gel	2	10	8	17
10	solution	2	10	5	14
11	solution	4	10	7	12
12	solution	6	10	4.2	2.9

* Ethanol/PG/Water mixing weight ratio 70:10:20.

Example 2

This example compares the percutaneous absorption of progesterone through human skin from 1% or 2% gel formulations with and without skin penetration enhancer (2-n-nonyl-1,3-dioxolane, 2-NND) in the aqueous alcoholic gel formulation using an ethanol:propylene glycol:water vehicle at a 70:20:10 or 70:10:20 weight mixing ratio. The compositions used in these tests are shown in the following Table 2. Hydroxypropyl cellulose (2 wt.%) is used as the gelling agent in the gel formulations. The test compositions are applied to provide about 30 milligrams (mg) of the composition per square centimeter (cm^2) of human skin.

The tests are run in standard static cells with phosphate buffered saline (PBS) and ethanol mixture (80:20) as the receptor fluid (surface area 0.635 cm^2, temperature 32°C).

Table 2

	progest-erone (%)	2-NND (%)	Vehicle (%)	Vehicle Composition	peak flux $\mu g/cm^2/h$	% of dose 24 hr
1	2	0	98	70:20:10 EtOH/PG/H2O	4.3	2.48
2	2	5	93	70:20:10 EtOH/PG/H2O	4.4	14.07
3	2	5	93	70:10:20 EtOH/PG/H2O	4.2	13.22
4	1	5	94	70:20:10 EtOH/PG/H2O	3.6	9.00

Example 3

This example is similar to Example 2 but comparing formulations with 2% progesterone and either 10% of enhancer (2-NND) or without enhancer in aqueous gel formulations containing Ethanol:PG:Water carrier at a 70:20:10 mixing weight ratio. The test conditions are, otherwise, the same as described in Example 2. The tested formulations and results are shown in Table 3.

Table 3

#	Enhancer (2-NND) (%)	Peak Flux $\mu g/cm^2/hr$	24 Hour Percent of Dose
1	0	6	6
2	10	8	17

Example 4

This example shows the results for a topical aqueous alcoholic gel formulation according to the present invention for the transdermal delivery of estradiol in comparison to the formulation of a commercially available estradiol-containing patch. The topical gel according to the present

invention contained 0.06% estradiol whereas the patch formulation contained 0.1 wt.% estradiol. The tests were run under the same conditions as described in Example 2.

In this example the "patch" formulation was obtained from an Estraderm® 0.1 patch which nominally delivers 100 micrograms of estradiol per day when applied twice per week. An appropriate amount of gel was removed from the Estraderm patch and used in the tests. The results for cumulative delivery of the patch formulation for 24 hours is calculated on the basis of 3.5 day delivery per patch. Although the patch is designed to meter the dose over the desired period (3.5 days) via an attenuating membrane, in the subject *in vitro* tests on human skin, the gel was applied without the membrane component of the Estraderm patch. All of the gels were essentially depleted of estradiol within 24 hours as apparent from the flux at 24 hours < 0.5 $\mu g/cm^2/hr$. The results obtained from the static cell *in vitro* tests run under the same conditions as previously described are shown in the following Table 4:

Table 4

Estradiol Formula	Peak Flux $\mu g/cm^2/hr$	Cumulative delivery at 24 hr. $\mu g/cm^2$	Cumulative delivery at 24 hr. μg	Cumulative amount at 24 hr % of dose
Invention: 0.06% drug 5% 2-NND E:PG:W = 70:20:10	0.2	2.0 ± .5	1.3 ± 0.3	10.4 ± 2.1
Estraderm, non-occluded	0.3	2.8 ± 1.4	1.8 ± 0.9	0.6 ± 0.3
Estraderm, occluded	3.0	23.8 ± 6.1	15.1 ± 3.9	4.4 ± 1.1

In the above Table 4 the non-occluded Estraderm gel was used without the protective cover layer provided with the commercial product, whereby the volatile solvents are allowed to evaporate. In the occluded Estraderm gel the protective cover layer was maintained over the gel to inhibit evaporation of the volatile solvents.

The following Table 5 provides a comparison between the obtained and expected results for the Estraderm gel (occluded) and the gel of the present invention by taking into consideration the actual patch delivery area (20 cm^2) and the recommended 3.5 day (2 per week) patch delivery cycle.

Table 5

	Estraderm (occluded)	Invention Gel
Estradiol (%)	1.8	0.06
Amount Applied (mg gel/0.635 cm^2)	20.13	20.19
Amount Applied, this study (mg gel/cm^2)	31.7	31.8
Amount Applied, intended (mg gel/cm^2)	22.3	10.0
In Vitro Transdermal Delivery ($\mu g/cm^2/24h$)	23.8	2.0
84 or 24 hr Amt delivered (μg(est.)/20 cm^2)	475.4	40.0
24 hr Amt delivered (μg(est.)/20 cm^2)	135.8	40.0
Adjusted 24 hr Amt. delivered (μg(est)/20 cm^2)*	95.5	40.0
Equivalent Amt. delivered IF: (1.0 g. Invention Gel/100 cm^2)	-	62.9
Amt (g) of Invention Gel to apply to deliver 50 μg/day	-	0.8
Amt (g) of Invention Gel to apply to deliver 100 μg/day	-	1.6
Reported Delivery (Estraderm Product Brochure)	350	-
Observed delivery, 3.5 days, this study	334	-
Equivalent coverage area (cm^2)	20	100

= as found in this study

* = Difference in formulation amt. applied, Patch *in vivo* vs. this study

From the above results it may be appreciated that the gel formulation according to the present invention is substantially as or more effective as the commercially available reservoir patch estradiol product while providing ease of use, increased flexibility of use, less irritation and substantially lower cost based on active ingredient.

Example 5

This example compares the results of the same aqueous alcoholic topical gel estradiol formulation according to the present invention as used in Example 4 versus a control gel without the enhancer and a commercially available gel product, Oestragel®.

The results are shown in Figure 3 for cumulative amount of estradiol diffused through the human skin sample as a function of time. The cumulative amount of the estradiol is significantly higher for the invention formulation than for the control or commercial product.

Example 6

This example is designed to compare the influence of various glycol coenhancers on the percutaneous absorption of hormone (estradiol) using the following formulation:

Ingredient	wt. %
Estradiol	2
2-NND	10
Ethanol (70% aq.)	68
Glycol Coenhancer	20

in *in vitro* tests on human skin using the same test cells as described in Example 1. The results are shown in the following Tables 6 and 7.

Table 6

Run No.	Coenhancer	% of dose delivered at 24 hr.
1	1,2-butylene glycol	2.78
2	1,2-hexylene glycol	2.01
3	1,2-propylene glycol	1.88
4	1,3-propylene glycol	1.21
5	Ethylene glycol	0.97
6	1,2-dodecanediol	0.90

Table 7

Run No.	Coenhancer	% of dose delivered at 24 hr.
1	1,2-propylene glycol	1.68
2	Glycerol (1,2,3-propanetriol)	0.45

Table 6 shows the superior performance of 1,2-diols having from 3 to 6 carbon atoms. Table 7 shows the superior performance of the 1,2-diol as compared to a triol with the same number of carbon atoms.

Example 7

This example shows the effectiveness of the invention topical formulations for transdermal delivery of testosterone. In particular, this example shows the results for a topical aqueous alcoholic gel formulation according to the present invention for the transdermal delivery of testosterone in comparison to the gel formulation removed from a commercially available testosterone-containing patch (Androderm®). The topical gel according to the present invention contained 10 wt.% 2-NND and an ethanol/1,2-propylene glycol/water vehicle at a 70:20:10 ratio. The tests were run under the same conditions as described in Example 2 using each of the gels in equal amounts in terms of a finite dose of testosterone. An appropriate amount of gel was removed from the Androderm patch and used in the

tests. The results for cumulative delivery of the patch formulation for 24 hours is calculated on the basis of 3.5 day delivery per patch. Although the patch is designed to meter the dose over the desired period (3.5 days) via an attenuating membrane, in the subject *in vitro* tests on human skin, the gel was applied without the membrane component of the patch. The results obtained from the static cell *in vitro* tests run under the same conditions as previously described are shown in Figure 5. As can be readily seen from Fig. 5, the gel of the present invention is more efficient (higher percent delivery of testosterone) than the occluded and non-occluded gel of the Androderm commercial product.

What is claimed is:

Claim 1. An alcoholic or aqueous alcoholic topical composition for the transdermal delivery of a hormonally active drug which comprises, on a weight basis, of the total composition:

from about 0.1 to about 10% of hormonally active drug;

from about 2 to 20% of skin penetration enhancer comprising C_7 to C_{14}-hydrocarbyl substituted 1,3-dioxolane, 1,3-dioxane or acetal;

0 to about 25% of propylene glycol;

from about 35% to 75% of volatile alcohol selected from the group consisting of ethanol, isopropanol and mixture thereof;

0 to about 35% water; and,

optionally, a gelling agent effective to thicken the composition to avoid or minimize run-off when applied to the skin.

Claim 2. The topical composition according to Claim 1 wherein said gelling agent is present and comprises up to about 4% of cellulosic thickener.

Claim 3. The topical composition according to claim 2 which comprises on a weight basis:

from about 1 to about 6% of hormonally active drug;

from about 2 to 15% of said enhancer;

5 to about 22% 1,2-propylene glycol;

from about 40 to 75% ethanol, isopropanol or mixture thereof;

0 to about 25% water; and,

0 to about 3% of cellulosic thickener.

Claim 4. The topical composition according to claim 2 which comprises, on a weight basis:

from about 1.0 to about 4% of hormonally active drug;

from about 5 to 10% of said enhancer;

5 to about 20% 1,2-propylene glycol;

from about 50 to 75% ethanol, isopropanol or mixture thereof;

0 to about 25% water; and,

0 to about 2% of cellulosic thickener.

Claim 5. The topical composition according to claim 2 wherein the hormonally active drug is an estrogen, progesterone or androgen or mixture thereof.

Claim 6. The topical composition according to claim 5 wherein the hormonally active drug comprises testosterone.

Claim 7. The topical composition according to claim 5 wherein the hormonally active drug comprises an estradiol.

Claim 8. The topical composition according to claim 5 wherein the hormonally active drug comprises progesterone.

Claim 9. The topical composition according to claim 6 comprising an ethanol/propylene glycol/water carrier system at a weight ratio of 70:10-20:20-10; and about 10% by weight of 2-n-nonyl-1,3-dioxolane.

Claim 10. The topical composition according to claim 7 comprising an ethanol/propylene glycol/water carrier system at a weight ratio of 70:10-20:20-10; and from about 5 to about 10% by weight of 2-n-nonyl-1,3-dioxolane.

Claim 11. The topical composition according to claim 13 comprising about 10 percent by weight of 2-n-nonyl-1,3-dioxolane.

Claim 12. The topical composition according to claim 8 comprising an ethanol/propylene glycol/water carrier system at a weight ratio of 70:10-20:20-10; and from about 5 to about 10% by weight of 2-n-nonyl-1,3-dioxolane.

Claim 13. The topical composition according to claim 15 comprising about 10 percent by weight of 2-n-nonyl-1,3-dioxolane.

Claim 14. A method for the transdermal administration of hormonally active drug to a patient in need thereof which comprises

topically applying to the skin of the patient an alcoholic or aqueous alcoholic composition comprising a therapeutically effective amount of hormonally active drug in a vehicle comprising a lower alcohol selected from the group consisting of ethanol, isopropanol and mixture

thereof, 1,2-alkyl diol having from 3 to 6 carbon atoms, and water in a mixing ratio of alcohol:glycol:water of 50-80:5-20:5-40, said vehicle comprising from about 70 to 90 weight percent of the composition, and from about 5 to about 20 weight percent of a skin penetration enhancing compound selected from the group consisting of 2-hydrocarbyl-1,3-dioxolane, 2-hydrocarbyl-1,3-dioxane and hydrocarbyl substituted-acetal, wherein the hydrocarbyl group has from 7 to 14 carbon atoms.

Claim 15. The method for the transdermal administration of a hormonally active drug according to claim 9 wherein the hormonally active drug is selected from the group consisting of estrogen, progesterone, androgen or mixture thereof.

Claim 16. The method for the transdermal administration of hormonally active drug according to claim 9 wherein the drug is selected from the group consisting of testosterone, progesterone and estradiol.

Claim 17. The method according to claim 9 wherein the hormonally active drug is testosterone.

Claim 18. The method according to claim 9 wherein the hormonally active drug is estradiol.

Claim 19. The method according to claim 9 wherein the hormonally active drug is progesterone.

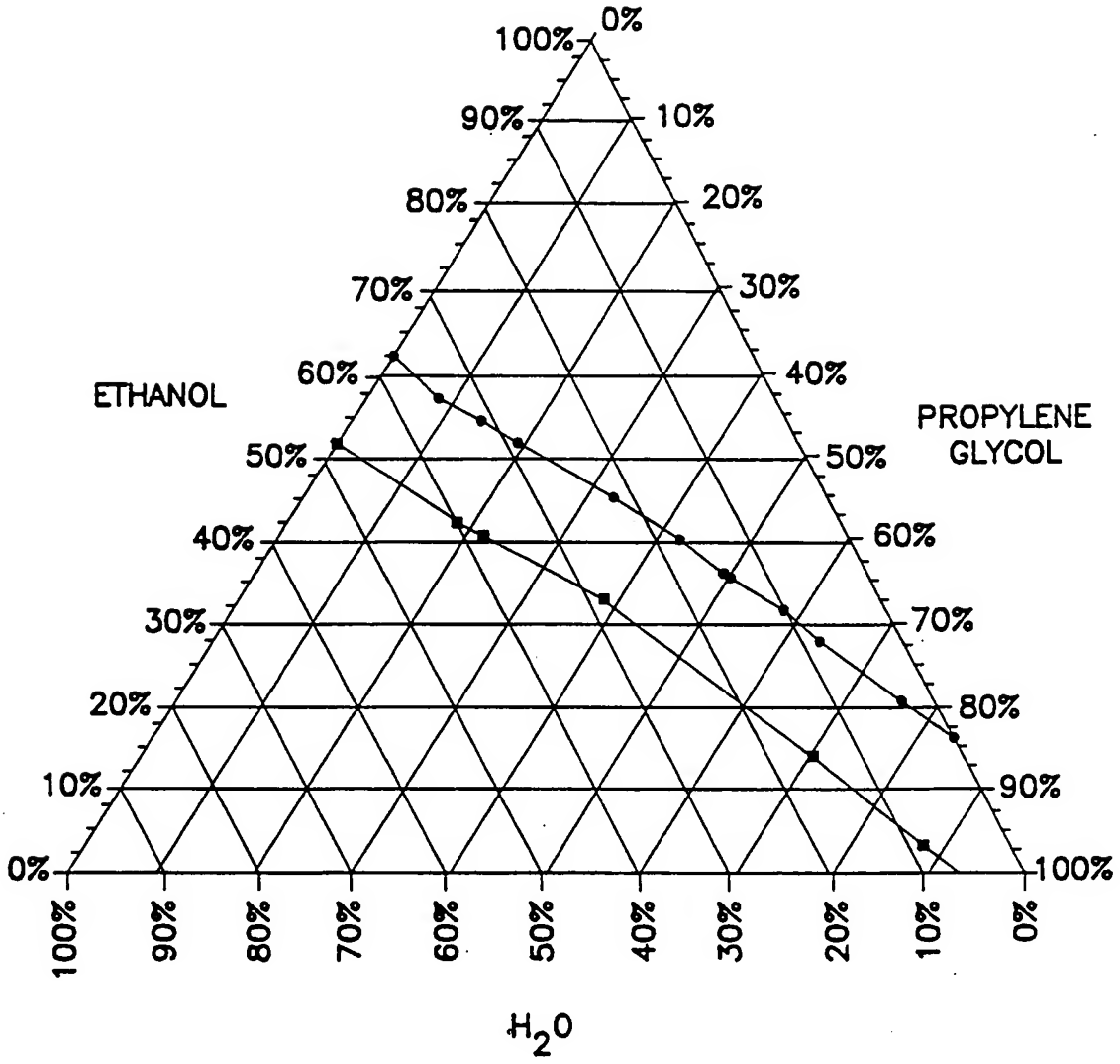
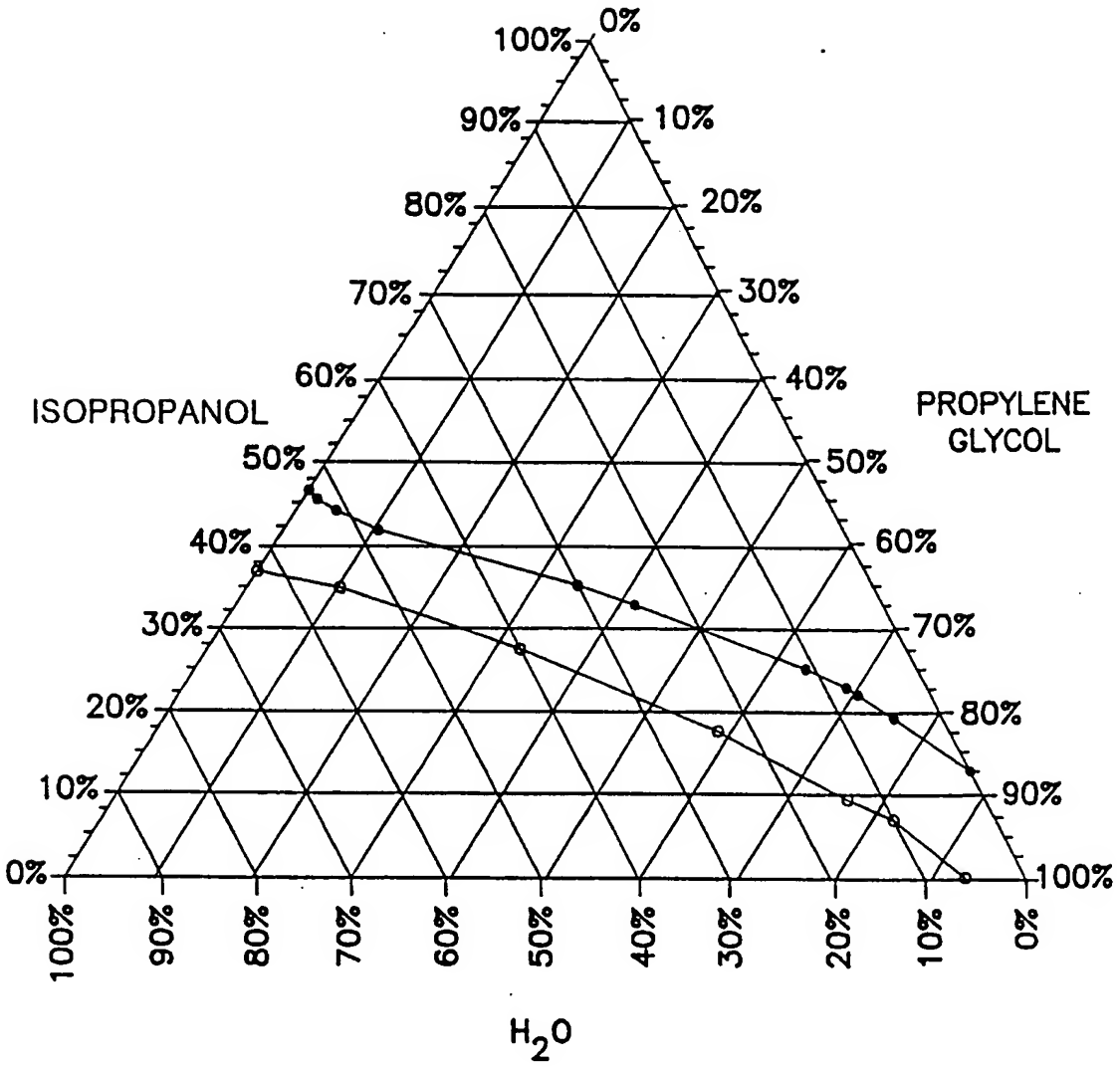


FIG. 1


ISOPROPANOL
PROPYLENE GLYCOL
H_2O
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90%
80%
70%
60%
50%
40%
30%
20%
10%
0%

FIG. 2

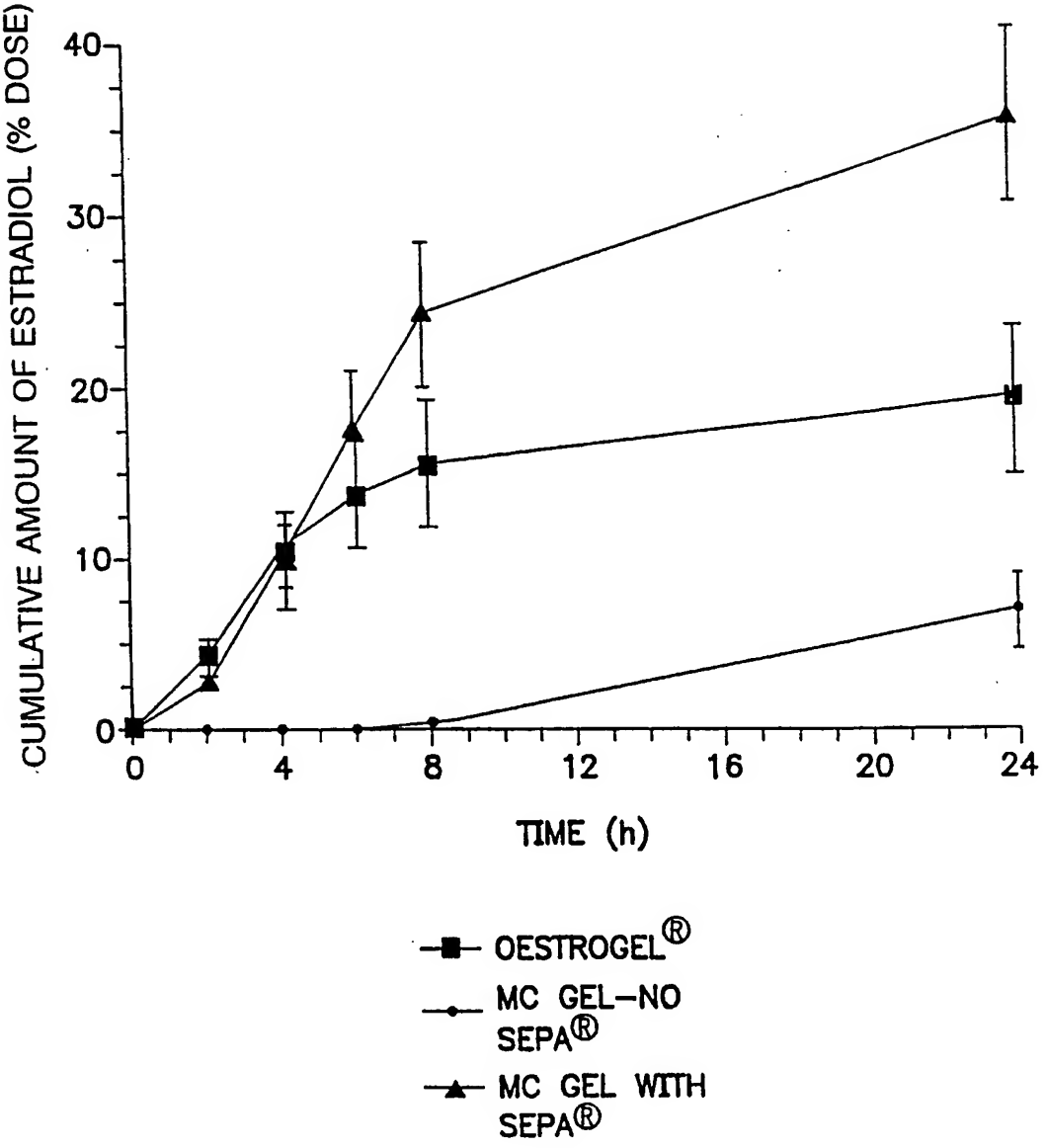
CUMULATIVE AMOUNT OF ESTRADIOL (% DOSE)
40
30
20
10
0
0
4
8
12
16
20
24
TIME (h)
OESTROGEL®
MC GEL–NO SEPA®
MC GEL WITH SEPA®

FIG. 3

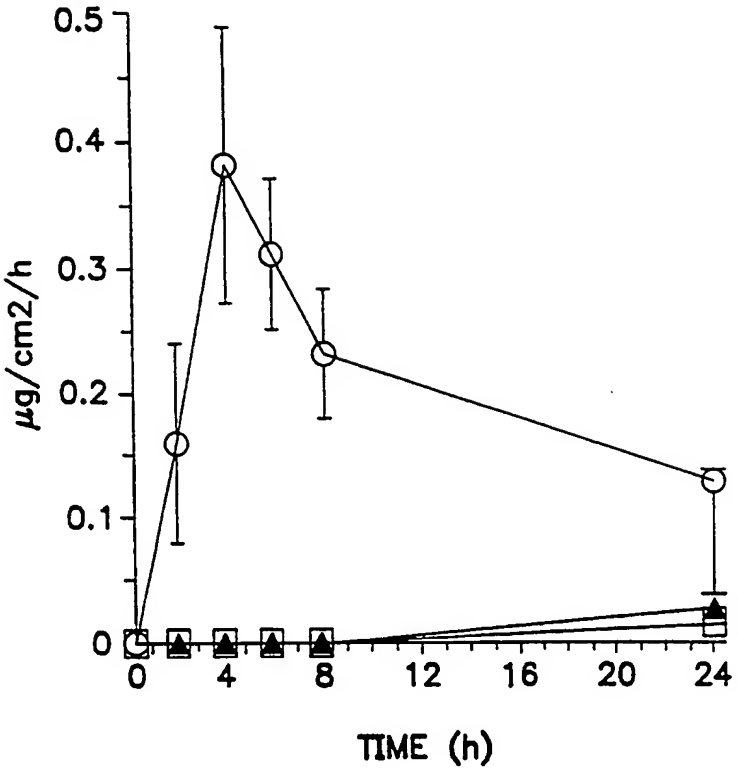
0.5
0.4
0.3
0.2
0.1
0
µg/cm2/h
0
4
8
12
16
20
24
TIME (h)

FIG. 4A

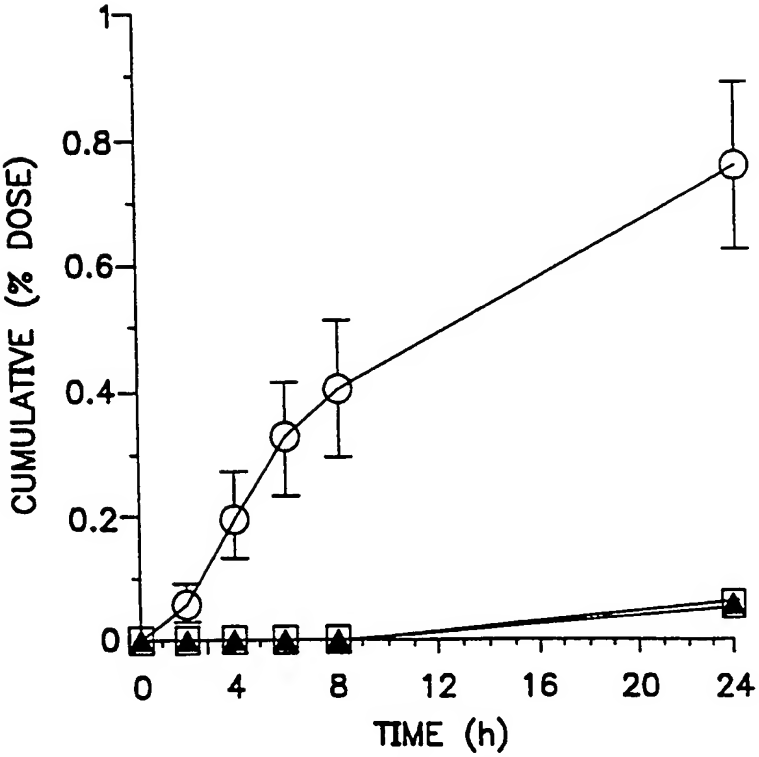
1
0.8
0.6
0.4
0.2
0
CUMULATIVE (% DOSE)
0
4
8
12
16
20
24
TIME (h)

FIG. 4B

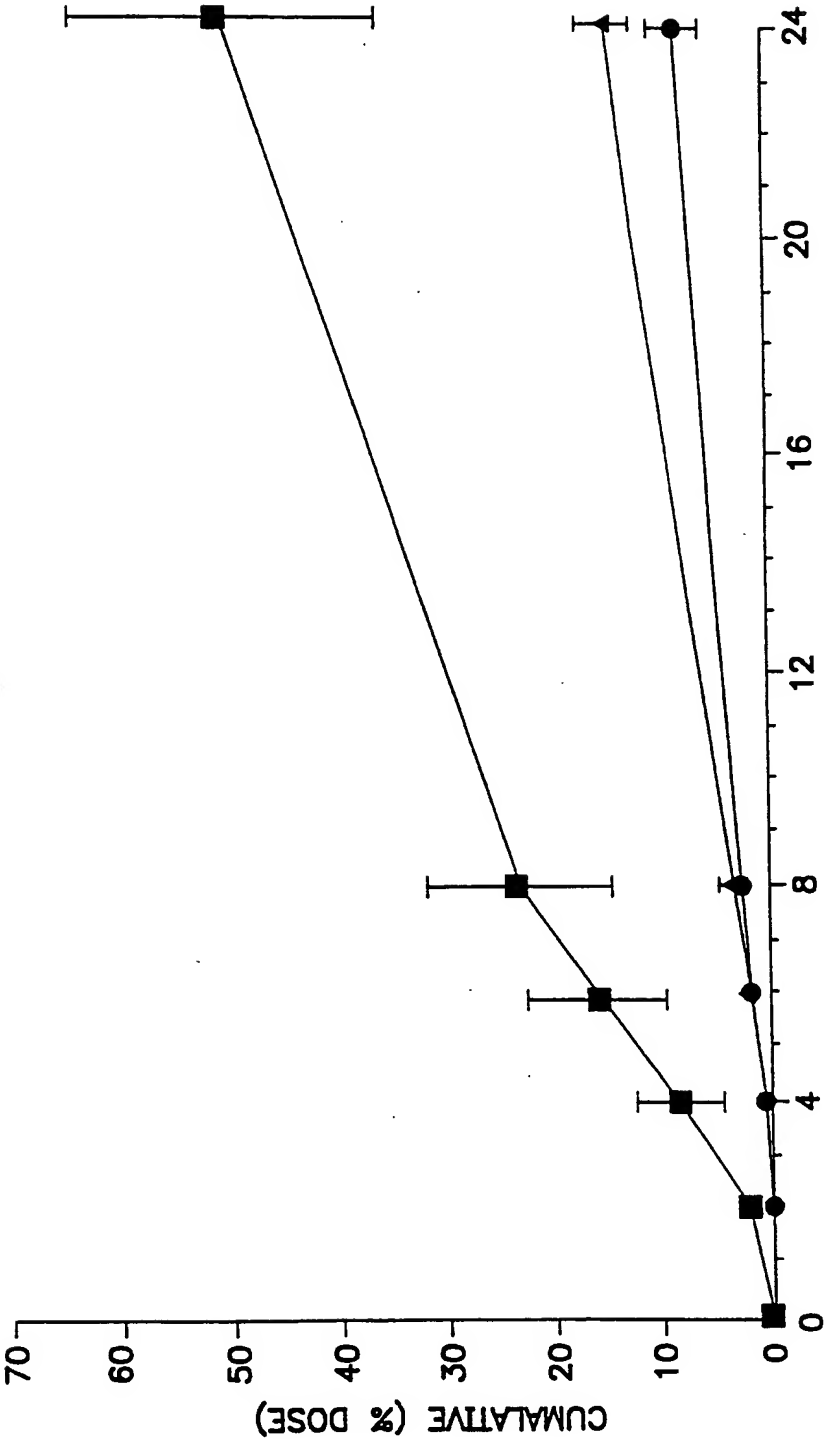

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/20895

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/70
US CL :424/456, 449

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/456, 449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

chemical abstracts

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,861,764 A (SAMOUR et al) 29 August 1989, see entire document.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search 13 JANUARY 1999	Date of mailing of the international search report 03 FEB 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JAMES H. REAMER Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

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(71) Anmelder *(für alle Bestimmungsstaaten mit Ausnahme von US)*: HEXAL AG [DE/DE]; Industriestrasse 25, D-83607 Holzkirchen (DE).

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(81) Bestimmungsstaaten *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Bestimmungsstaaten *(regional)*: ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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— *mit internationalem Recherchenbericht*

(88) Veröffentlichungsdatum des internationalen Recherchenberichts: 11. Oktober 2001

Zur Erklärung der Zweibuchstaben-Codes, und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: PHARMACEUTICAL GEL CONTAINING ACTIVE SUBSTANCES

(54) Bezeichnung: PHARMAZEUTISCHES, WIRKSTOFFHALTIGES GEL

(57) Abstract: The invention relates to a topically applied pharmaceutical gel which contains active substances and which has topical or systemic action, whereby the use of an otherwise common short-chain monovalent alcohol is forgone. In addition to having a very good activity, a formulation of this type can prevent skin irritations, skin damages or skin sensitivities. A particular embodiment of the invention depicts an emulsion gel for treating inflammatory skin diseases. This embodiment contains phospholipids and/or natural vitamin E and/or α-tocopherol and/or α-tocopherol derivatives, preferably α-tocopherol acetate as well as at least one corticosteroid, preferably prednicarbate. The gel is used to treat inflammatory skin diseases such as atopic dermatitis or neurodermatitis, psoriasis, acute and chronic eczema, burns and contact eczema. Another embodiment of the invention depicts an emulsion gel for systemically administering hormones containing phospholipids and/or α-tocopherol and/or α-tocopherol derivatives and at least one estrogen, preferably estradiol.

(57) Zusammenfassung: Die Erfindung betrifft ein topisch zu applizierendes, pharmazeutisches, wirkstoffhaltiges Gel mit topischer oder systemischer Wirkung, wobei auf einen sonst üblichen kurzkettigen, einwertigen Alkohol verzichtet werden kann. Neben einer sehr guten Wirksamkeit können mit einer derartigen Formulierung Hautirritationen, Hautschäden oder Hautsensibilisierungen vermieden werden. Eine besondere Ausführungsform der Erfindung stellt ein Emulsionsgel zur Behandlung von entzündlichen Hauterkrankungen dar, beinhaltend Phospholipide und/oder natürliches Vitamin E und/oder α-Tocopherol und/oder α-Tocopherol-Derivate, bevorzugt α-Tocopherolacetat, sowie mind. ein Corticosteroid, bevorzugt Prednicarbat. Unter entzündlichen Hauterkrankungen werden hier Erkrankungen wie atopische Dermatitis oder Neurodermitis, Psoriasis, akute und chronische Ekzeme, Verbrennungen und Kontaktekzeme verstanden. Eine weitere Ausführungsform der Erfindung stellt ein Emulsionsgel zur systemischen Verabreichung von Hormonen, beinhaltend Phospholipide und/oder α-Tocopherol und/oder α-Tocopherol-Derivate sowie mind. ein Östrogen, bevorzugt Estradiol, dar.

WO 01/21153 A3

INTERNATIONAL SEARCH REPORT

Intern. ial Application No
PCT/EP 00/09059

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 393 904 A (MAXAM, INC.) 24 October 1990 (1990-10-24) page 2, line 4 - line 8 page 3, line 30 - line 36 page 5; example 1; table 1	1,8,13
X	EP 0 347 225 A (CHINOIN) 20 December 1989 (1989-12-20) page 8; examples 4,6	1,2,8, 11,13, 14,22,23
X	WO 96 29988 A (ROENTSCH ET AL.) 3 October 1996 (1996-10-03)	1-3,5,8, 9,12-15, 18,21-23
Y	the whole document	4,10,19
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 April 2001	03/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

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INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/EP 00/09059

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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E	WO 00 56366 A (PARKER HUGHES INSTITUTE) 28 September 2000 (2000-09-28) page 8, line 1 -page 11, line 25 page 48, line 6 - line 27 -----	1-3, 11-14, 22,23

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. ial Application No
PCT/EP 00/09059

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INTERNATIONALER RECHERCHENBERICHT

Interna ales Aktenzeichen
PCT/EP 00/09059

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 7 A61K9/06

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 7 A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)
WPI Data, PAJ, EPO-Internal

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
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[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

° Besondere Kategorien von angegebenen Veröffentlichungen :
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°&° Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der Internationalen Recherche	Absendedatum des Internationalen Recherchenberichts
24. April 2001	03/05/2001

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

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C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

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